II. Remarks

A. Amendments to the Claims and Formal Matters

Claims 62, 66-71 and 75-82 and 87-93 are pending and under active consideration in the application. Claims 87 and 90-92 have been withdrawn by the Examiner. Claim 62 is amended. Upon entry of these amendments, claims 62, 66-71, 75-82 and 87-93 will be pending with claims 62, 66-71, 75-82, 88-89 and 93 under active consideration. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application.

Applicant respectfully submits that no new matter has been added by the amendment.

B. Patentability Rejections

1. The Rejections Under 35 U.S.C. §112, First Paragraph – Enablement – Should be Withdrawn

a. Claims 62, 66-71, 75-82 and 93

Claims 62, 66-71 and 75-82 and 93 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking an enablement for the full scope of the invention. According to the Examiner:

> ...as the polypeptide claimed in claim 62 comprises the sequence of SEQ ID NO: 2, other type I IFN receptors cannot be excluded, and hence encompass isolated and mutated polypeptide sequences of numerous receptor variants of the type I IFN receptors, such as membrane bound, cytoplasmic or soluble forms. Therefore, while the enabled scope of (sic) may not extend to polypeptides which do not retain the synergistic increase in affinity for IFN-β, the claimed scope clearly does.

The Examiner bears the initial burden of showing nonenablement. *See In re Wright*, 999 F.2d 1557, 1561-1562 (Fed. Cir. 1993). "[E]nablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.'...That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d 488,

495 (Fed. Cir. 1991) (emphasis in original). Some experimentation, even a considerable amount, is not "undue" if e.g., it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Applicants respectfully submit that the Examiner has failed to set forth a *prima facie* case of lack of enablement.

As a preliminary matter, Applicants direct the Examiner's attention to SEQ ID NO: 2. SEQ ID NO: 2 represents the amino acid sequence of the extracellular domain of IFNAR2 and contains alanine substitutions at positions 78 and 100. This polypeptide is demonstrated, as a working embodiment, to exhibit synergistically increased affinity for IFN-β. A polypeptide comprising SEQ ID NO: 2, as claimed, necessarily comprises the sequence demonstrated by the instant specification to exhibit increased affinity for IFN-β. Accordingly, the pending claims encompass "other type I IFN receptors" only to the extent that such receptors comprise SEQ ID NO: 2. The Examiner has simply not provided any basis for concluding that such receptors "do not retain the synergistic increase in affinity for IFN-β."

At page 4 of the Final Office Action, the Examiner concludes that:

> it remains unknown whether the mutations of his 78 and asp 100 in SEQ ID NO: 2 would retain their synergistic increase in binding IFNβ, following a fusion to any of numerous unknown amino acid sequences of unlimited size, that can introduce substantial variation, affecting binding of IFNβ.

Applicants respectfully submit that the scope of the claim 62 and dependent claims 66-71, 75-82 and 93 **does not extend** to polypeptides lacking synergistically increased affinity for IFN-β. The Examiner has improperly read this limitation out of the claim. According to MPEP 2173.05(g), "[t]here is nothing inherently wrong with defining some part of an invention in functional terms...[a] functional limitation **must be evaluated and considered, just like any other limitation** of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used" (emphasis added). When properly construed, the scope of the pending claims does not extend to the hypothetical polypeptides referred to by the Examiner.

The instant specification describes binding assays by which one of ordinary skill in the art can identify those polypeptides which exhibit the claimed synergistically enhanced affinity for IFN-β. *See, e.g.*, specification, paragraph [0090]. One of ordinary skill in the art would, in view of the disclosure provided by the instant Application, and of common general knowledge at the time the present Application was filed, make the claimed polypeptides and identify those polypeptides which exhibit the claimed synergistically enhanced affinity for IFN-β without recourse to undo experimentation. Accordingly, Applicants respectfully submit that the full scope of claims 62, 66-71, 75-82 and 93 is enabled by the present disclosure and request that the Examiner withdraw the rejection of claims 62, 66-71, 75-82 and 93 for lack of enablement.

b. Claims 88 and 89

Claims 88 and 89 stand rejected under 35 U.S.C. §112 for an alleged lack of enablement for the reasons of record. Applicant respectfully traverses.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). In determining whether a disclosure satisfies the enablement requirement (and whether any necessary experimentation is "undue") the Examiner should consider the *Wands* factors. It is improper for the Examiner to conclude that a disclosure is not enabling based on analysis of only one of the *Wands* factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands*, 858 F.2d at 737, 740. A determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the factual considerations set forth by the Federal Circuit in *In re Wands*. *See also* MPEP 2164.01(a).

i. <u>The Level of Skill in the Art is High</u>

The relative skill of those in chemical and biological arts is high. Methods of making the claimed polypeptides were known in the art and the experimentation involved

to use the claimed polypeptides in accordance with the full scope of claims 88 and 89 would have been well within the skill of those in the art and therefore would have been routine.

ii. The State of the Art

The activity of type I interferons in modulating the immune system was known and it was known that type I interferons act through a cell surface receptor complex to induce such a biological effect. See specification, pages 1-2, paragraphs [0005]-[0006].

European Patent No. EP1037658B, at Example 11, proves that injection of mice with IFN-β complexed to soluble wild type IFNAR2 enhances the serum half life of IFN-β. Importantly, similar enhancement of the serum half life of IFN-β was observed following an injection of IFN-β followed by a second, separate injection of soluble wild type IFNAR2 (sIFNAR2). Thus, EP1037658 demonstrates the ability of administered sIFNAR2 to complex *in vivo* with circulating IFN-β. Moreover, such enhanced half life is demonstrated to result in enhancement and prolongation of IFN-mediated efficacy *in vivo* and such activity would be useful in any disease, such as multiple sclerosis, in which IFN-β itself is active. *See* EP1037658 at Example 14. Importantly, intrathecal administration of the type I interferon IFN-β has been demonstrated to reduce the exacerbations of multiple sclerosis. *See* specification, page 4, paragraph [0010].

iii. The Presence or Absence of Working Examples

The present disclosure, at Examples 4 and 7 and Figure 4, provides working examples demonstrating enhanced activity of IFN-β/IFNAR2 (wild type and mutant) complexes relative to free IFN-β. In the experiments, the addition of IFNAR2 to a constant amount of IFN-β resulted in a dose-dependent increase in cell survival upon challenge with vesicular stomatitis virus (VSV). As cell survival is dependent on IFN-β activity, such a result demonstrates that addition of IFNAR2 stabilizes and enhances the activity of IFN-β. Importantly, for its use as a carrier of IFN-β, a significantly lower concentration of the claimed polypeptides is required relative to the wild type sIFNAR2 due to the synergistic increase in affinity for IFN-β resulting from the claimed mutations. As shown by EP1037658, these *in vitro* results correlate with an enhancement and

prolongation of IFN-mediated efficacy *in vivo* and are applicable to any therapeutic indication in which free IFN-β has shown therapeutic activity, such as multiple sclerosis.[1]

iv. The Evidence, When Properly Considered in its Entirety, Compels a Finding that the Full Scope of Claims 88 and 89 are Enabled.

Applicants respectfully submit that the instant disclosure, along with knowledge in the art at the time of filing, provides the guidance necessary to enable the full scope of claims 88 and 89 in view of at least (1) the working examples of the instant specification demonstrating that the claimed polypeptides are superior carrier molecules for IFN-β and enhance the activity of IFN-β *in vitro*; (2) the state of the art which demonstrates that wild type sIFNAR2 acts as a carrier molecule for IFN-β *in vivo* following its injection resulting in prolonged and enhanced IFN-β activity; and (3) the high level of skill in the art allowing the routine determination of adjustments and manipulations of the disclosed optimal range of claimed polypeptide (0.24 nM – 0.4 nM) to achieve the claimed methods.

[1] In fact, the same ratio as used to maximize the generation of active complex *in vitro* resulted in elongated pharmacokinetics of IFN-β *in vivo*. *See* EP1037658 at page 13, lines 7-9 (citation is made with reference to WO 99/32141, an equivalent document).

2. The Rejections Under 35 U.S.C. §103(a) Should be Withdrawn

a. Claims 62, 66-71 and 75-76

Claims 62, 66-71 and 75-76 stand rejected under 35 U.S.C. §103(a) over Piehler *et al.* ("Piehler"). Applicant respectfully traverses the rejection and requests reconsideration in view of the remarks below.

The Examiner acknowledges the unpredictability of combining two known mutations: "[i]f the outcome of the double mutation could be accurately predicted, it would not be 'interesting' to explore such a result." When combining two mutations there are three possible outcomes: (1) the combination could be additive (the effect predicted by mass-action law principle in the absence of synergism or antagonism) in which case about a 6-fold increase in affinity for IFN-β would be expected (2) the combination could be antagonistic (reduced affinity for IFN-β than the expected additive effect based on mass-action law) or (3) the combination could be synergistic (greater affinity for IFN-β than the expected additive effect based on mass-action law). Of these possible results, only the first can be reasonably expected and such expectation derives from the law of mass-action. Contrary to the Examiner's assertions, there is simply no suggestion in Piehler that the mutations would synergistically increase affinity for IFN-β.

According to the Examiner, "[w]hen the teachings of Piehler are considered in total, there is no basis for predicting an absence of synergy between the two mutations in increasing the affinity of the ifnar2 receptor for IFN-β." Applicant is baffled by this statement. As discussed above, Piehler does not teach or suggest a synergistic increase in affinity for IFN-β in a H78A/N100A double mutant, nor has the Examiner pointed to any such teaching in the prior art. The literature is rife with examples of combinations of mutations, separately shown to have some effect on polypeptide function, having additive or antagonistic effects on that function when expressed together. One of ordinary skill in the art, understands that a synergistic effect in combining two separate mutations is not the *expected* result.

Piehler is concerned with mutations that increase the affinity of IFNAR for IFNβ. The only prediction made by Piehler is that the H78A/N100A double mutant should exhibit 20-fold tighter binding for IFNβ compared to IFNα2. However, the affinity of

the claimed double mutant was shown to be about 100 times higher than the wild type towards IFNβ and unchanged towards IFNα2, in stark contrast to the prediction of Piehler. This constitutes additional probative evidence of the unexpected nature of the claimed polypeptide.

According to the Examiner, "the product must necessarily possess an increased affinity for IFN-β, as Piehler et al. show increased affinities...for each of the separate mutations, with the N100A mutation hardly affecting the rate of IFNa2 binding." As discussed above, no such expectation can be discerned from Piehler. The Examiner has failed to explain why the double mutant "must necessarily possess" an increased affinity for IFN-β. It is possible that the double mutant could have possessed a decreased affinity for IFN-β relative to the wild type polypeptide. Regardless, what is demonstrated and claimed is an unexpected synergistic increase in affinity for IFN-β, not simply an increased affinity and such is not predicted by Piehler.

According to MPEP § 716.02(a), a demonstration of synergy is sufficient to overcome a *prima facie* case of obviousness where the results obtained are greater than those which could have been expected from the prior art to an unobvious extent and the results are of significant, practical advantage. In light of the unexpected, claimed synergistic increase, no indication of which is disclosed by Piehler and which could not have been obvious to the ordinary artisan, Applicant respectfully requests that the rejection for obviousness be reconsidered and withdrawn.

b. Claims 77-82

At page 9 of the Final Office Action, the Examiner maintains his rejection of claims 77-81 under 35 U.S.C. §103(a) over Piehler and Campbell *et al.* ("Campbell") and applied this rejection to claim 82 as well. As discussed above, Piehler fails to teach or suggest the synergistic effect of the claimed double mutant H78A/N100A. Campbell, characterized by the Examiner as describing fusion protein constructs containing the hGH signal peptide in place of the native signal sequence of proteins, does nothing to remedy the defect of Piehler. Accordingly, Applicant respectfully requests that the rejection for obviousness be reconsidered and withdrawn.

C. Conclusion

In view of the above amendments and remarks, Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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